

- 1. A substantially pure preparation of a cell cycle regulatory (CCR) protein, or a fragment thereof, which specifically binds to a cyclin-dependent kinase (CDK), the full-length form of said CCR-protein having an approximate molecular weight in the range of 14.5kD to 16kD.
- 2. The CCR-protein of claim 1, comprising an amino acid sequence at least 60% homologous to an amino acid sequence represented in SEQ ID No. 2.
- 3. The CCR-protein of claim 1, comprising an amino acid sequence at least 60% homologous to an amino acid sequence represented in SEQ ID No. 4.
- 4. The CCR-protein of claim 1, including an amino acid sequence represented by the general formula:

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Met-Met-Gly-Xaa-Xaa-Xaa-Val-Ala-Xaa-Leu-Leu-Leu-Xaa-Xaa-Gly-Ala-Xaa-Xaa-Asp-Cys-Xaa-Asp-Pro-Xaa-Thr-Xaa-Xaa-Xaa-Arg-Pro-Val-His-Asp-Ala-Ala-Arg-Glu-Gly-Phe-Leu-Asp-Thr-Leu-Val-Val-Leu-His-Xaa-Xaa-Gly-Ala-Arg-Leu-Asp-Val-Arg-Asp-Ala-Trp-Gly-Arg-Leu-Pro-Xaa-Asp-Leu-Ala-Xaa-Glu-Xaa-Gly-His-Xaa-Asp-Xaa-Xaa-Tyr-Leu-Arg-Xaa-Ala-Xaa-Gly.
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- 5. The CCR-protein of claim 1, which CCR-protein functions in one of either role of an agonist of cell-cycle regulation or an antagonist of cell-cycle regulation.
- 6. A substantially pure preparation of a p15 polypeptide, or a fragment thereof, having an amino acid sequence at least 60% homologous to SEQ ID No. 4.
- 7. The polypeptide of claim 6 which specifically binds a cyclin dependent kinase (CDK).
- 8. The polypeptide of claim b, including an amino acid sequence represented by the general formula:

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Met-Met-Met-dly-Xaa-Xaa-Xaa-Val-Ala-Xaa-Leu-Leu-Leu-Xaa-Xaa-Gly-Ala-Xaa-Xaa-Asn-Cys-Xaa-Asp-Pro-Xaa-Thr-Xaa-Xaa-Xaa-Arg-Pro-Val-His-Asp-Ala-Ala-Arg-Glu-Gly-Phe-Leu-Asp-Thr-Leu-Val-Val-Leu-His-Xaa-Xaa-Gly-Ala-Arg-Leu-Asp-Val-Arg-Asp-Ala-Trp-Gly-Arg-Leu-Pro-Xaa-Asp-Leu-Ala-Xaa-Glu-Xaa-Gly-His-Xaa-Asp-Xaa-Xaa-Tyr-Leu-Arg-Xaa-Ala-Xaa-Gly.
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- 9. The polypeptide of claim 6, wherein said polypeptide which functions in one of either role of an agonist of cell cycle regulation.
- 10. An immunogen comprising the CCR-protein of claim 1, in an immunogenic preparation, said immunogen being capable of eliciting an immune response specific for said CCR-protein.

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An antibody preparation specifically reactive with an epitope of the immunogen of claim 10.

- 12. An immunogen comprising the polypeptide of claim 6 in an immunogenic preparation, said immunogen being capable of eliciting antibodies specific for said p15 polypeptide.
- 13. An antibody preparation specifically reactive with an epitope of the immunogen of claim 12.
- 14. A recombinant p15 polypeptide, or a fragment thereof, having an amino acid sequence at least 60% homologous to SEQ ID No. 4.
- 15. The polypeptide of claim 14, which p15 polypeptide functions in one of either role of an agonist of cell cycle regulation or an antagonist of cell cycle regulation.
- 16. The polypeptide of claim 14, which p15 polypeptide binds to a cyclin dependent kinase.
- 17. The polypeptide of claim 14, comprising an amino acid sequence represented by the general formula:

Met-Arg-Glu-Glu-Asn-Lys-Gly-Met-Pro-Ser-Gly-Gly-Gly-Ser-Asp-Glu-Gly-Leu-Ala-Thr-Pro-Ala-Arg-Gly-Leu-Val-Glu-Lys-Val-Arg-His-Ser-Trp-Glu-Ala-Gly-Ala-Asp-Pro-Asn-Gly-Val-Asn-Arg-Phe-Gly-Arg-Arg-Ala-Ile-Gln-Val-Met-Met-Met-Gly-Xaa-Xaa-Xaa-Val-Ala-Xaa-Leu-Leu-Leu-Xaa-Xaa-Gly-Ala-Xaa-Xaa-Asp-Pro-Xaa-Thr-Xaa-Xaa-Arg-Pro-Val-His-Asp-Ala-Arg-Glu-Gly-Phe-Leu-Asp-Thr-Leu-Val-Val-Leu-His-Xaa-Xaa-Gly-Ala-Arg-Leu-Asp-Val-Arg-Asp-Ala-Trp-Gly-Arg-Leu-Pro-Xaa-Asp-Leu-Ala-Xaa-Gly-Asp



- 18. The polypeptide of claim 14, wherein said polypeptide is cloned from a human cell.
- 19. The polypeptide of claim 14, wherein said polypeptide is a fusion protein further comprising, a second polypeptide portion having an amino acid sequence from a protein unrelated the protein of SEQ ID No. 4.
- 20. The polypeptide of claim 19, wherein said fusion protein is functional in a two-hybrid assay.
- 21. A substantially pure nucleic acid having a nucleotide sequence which encodes a cell cycle regulatory (CCR) protein, or a fragment thereof, which specifically binds a cyclin-dependent kinase (CDK), the full-length form of said CCR-protein having an approximate molecular weight in the range of 14.5kD to 16kD.
- 22. The nucleic acid of claim 21, wherein said CCR-protein encoded by said nucleotide sequence has an amino acid sequence at least 60% homologous to an amino acid sequence represented in SEQ ID No. 2.
- 23. The nucleic acid of claim 21, wherein said CCR-protein encoded by said nucleotide sequence has an amino acid sequence at least 60% homologous to an amino acid sequence represented in SEQ/D No. 4.
- 24. The nucleic acid of claim 21, wherein said CCR-protein encoded by said nucleotide sequence has an amino acid sequence represented by the general formula:

Met-Met-Met-Gly-Xaa-Xaa-Xaa-Val-Ala-Xaa-Leu-Leu-Leu-Xaa-Xaa-Gly-Ala-Xaa-Xaa-Asn-Cys-Xaa-Asp-Pro-Xaa-Thr-Xaa-Xaa-Xaa-Arg-Pro-Val-His-Asp-Ala-Ala-Arg-Glu-Gly-Phe-Leu-Asp-Thr-Leu-Val-Val-Leu-His-Xaa-Xaa-Gly-Ala-Arg-Leu-Asp-Val-Arg-Asp-Ala-Trp-Gly-Arg-Leu-Pro-Xaa-Asp-Leu-Ala-Xaa-Glu-Xaa-Gly-His-Xaa-Asp-Xaa-Xaa-Xaa-Tyr-Leu-Arg-Xaa-Ala-Xaa-Gly.

- 25. The nucleic acid of claim 21, wherein said CCR-protein encoded by said nucleotide sequence functions in one of either role of an agonist of cell cycle regulation or an antagonist of cell cycle regulation.
- 26. The nucleic acid of claim 21, wherein said nucleotide sequence hybridizes under stringent conditions to a nucleic acid probe corresponding to at least 12 consecutive nucleotides of either of SEQ ID No. 1 or SEQ ID No. 2.

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- 27. The nucleic acid of claim 21, further comprising a transcriptional regulatory sequence operably linked to said nucleotide sequence so as to render said nucleic acid suitable for use as an expression vector.
- 28. An expression vector, capable of replicating in at least one of a prokaryotic cell and eukaryotic cell, comprising the nucleic acid of claim 21.
- 29. A host cell transfected with the expression vector of claim 28 and expressing said polypeptide.
- 30. A method of producing a recombinant dell-cycle regulatory (CCR) protein comprising culturing the cell of claim 29 in a cell culture medium to express said CCR-protein and isolating said CCR-protein from said cell culture.
- 31. A transgenic animal having fells which harbor a transgene comprising the nucleic acid of claim 21.
- 32. A transgenic animal in which expression of a CCR-protein is disrupted in one or more tissue of said animal.
- 33. An recombinant gene comprising a nucleotide sequence at least 60% homologous to either of SEQ ID No. 1 or SEQ ID No.3, or a fragment thereof, said nucleotide sequence operably linked to a transcriptional regulatory sequence in an open reading frame and translatable to a polypeptide capable of functioning in one of either role of an agonist of cell cycle regulation or an antagonist of cell cycle regulation.
- 34. The recombinant gene of claim 33, which is derived from a cDNA clone.
- 35. The recombinant gene of claim 33, which is derived from a genomic clone and optionally includes intronic nucleotide sequences disrupting said opem reading frame.
- 36. The recombinant gene of claim 33, wherein said polypeptide is a fusion protein derived from at least two unrelated proteins, one of which includes a CDK-binding portion of SEQ ID No. 2 or SEQ ID No. 4.



- 37. An animal model for studying cellular disorders comprising a non-human animal in which at least one allelle of a gene encoding a protein represented by SEQ ID No. 4 is mutated or mis-expressed.
- 38. A probe/primer comprising a substantially purified oligonucleotide, said oligonucleotide containing a region of nucleotide sequence which hybridizes under stringent conditions to at least 10 consecutive nucleotides of sense or antisense sequence of SEQ ID No. 1 or SEQ ID No. 3, or naturally occurring mutants thereof.
- 39. The probe/primer of claim 38, further comprising a label group attached thereto and able to be detected.
- 40. A diagnostic test kit for identifying a transformed cell, comprising the probe/primer of claim 38, for measuring a level of nucleic acid encoding a cell-cycle regulatory protein in a sample of cells isolated from a patient.
- 41. A diagnostic test kit for identifying transformed cells, comprising an antibody specific for a p15 protein for measuring, in a sample of cells isolated from a patient, a level of said p15 protein.
- 42. A method of treating an animal having unwanted cell growth characterized by a loss of function of a cell-cycle regulatory (CCR) protein, comprising administering a therapeutically effective amount of an agent able to inhibit a kinase activity of a G₁ phase cyclin dependent kinase (CDK).
- 43. The method of claim 42, comprising administering a nucleic acid construct encoding a CCR-protein, or fragment thereof, under conditions wherein said construct is incorporated by CCR-deficient cells and the CCR-protein is expressed.
- 44. The method of claim 43, wherein said CCR-protein comprises an amino acid sequence represented by the general formula:

Met-Met-Met-Gly-Xaa-Xaa-Xaa-Val-Ala-Xaa-Leu-Leu-Leu-Xaa-Xaa-Gly-Ala-Xaa-Xaa-Asn-Cys-Xaa-Asp-Pro-Xaa-Thr-Xaa-Xaa-Arg-Pro-Val-His-Asp-Ala-Ala-Arg-Glu-Gly-Phe-Leu-Asp-Thr-Leu-Val-Val-Leu-His-Xaa-Xaa-Gly-Ala-Arg-Leu-Asp-Val-Arg-Asp-Ala-Trp-Gly-Arg-Leu-Pro-Xaa-Asp-Leu-Ala-Xaa-Glu-Xaa-Gly-His-Xaa-Asp-Xaa-Xaa-Xaa-Tyr-Leu-Arg-Xaa-Ala-Xaa-Gly.



- 45. The method of claim 43, wherein said CCR-protein comprises an amino acid sequence at least 60% homologous to an amino acid sequence represented in one of SEQ ID Nos. 2, 4 or 6.
- 46. The method of claim 42, comprising administering a peptidomimetic of a cell-cycle regulatory protein which binds to and inhibits the G₁ phase CDK.
- 47. A method of treating an animal having unwanted cell growth characterized by a loss of responsiveness of a population of cells to a transforming growth factor (TGF) protein, comprising administering a therapeutically effective amount of an agent able to inhibit a kinase activity of a G₁ phase cyclin dependent kinase (CDK).
- 48. The method of claim 47, comprising administering therapeutic amount of a CDK inhibitor selected from the group consisting of:
 - (i) a nucleic acid construct encoding a cell-cycle regulatory protein represented by the general formula.

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Met-Met-Met-Gly-Xaa-Xaa-Xaa-Val-Ala-Xaa-Leu-Leu-Leu-Xaa-Xaa-Gly-Ala-Xaa-Xaa-Asn-Cys-Xaa-Asp-Pro-Xaa-Thr-Xaa-Xaa-Xaa-Arg-Pro-Val-His-Asp-Ala-Ala-Arg-Glu-Gly-Phe-Leu-Asp-Thr-Leu-Val-Val-Leu-His-Xaa-Xaa-Gly-Ala-Arg-Leu-Asp-Val-Arg-Asp-Ala-Trp-Gly-Arg-Leu-Pro-Xaa-Asp-Leu-Ala-Xaa-Glu-Xaa-Gly-His-Xaa-Asp-Xaa-Xaa-Xaa-Tyr-Leu-Arg-Xaa-Ala-Xaa-Gly;
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- (ii) a nucleic acid construct encoding a cell-cycle regulatory protein comprising an amino acid sequence at least 60% homologous to an amino acid sequence represented in one of SEQ ID Nos. 2, 4 or 6; and
- (iii) a peptidomimetic of the cell-cycle regulatory protein of (a) or (b), which peptidomimetic binds to and inhibits the CDK.
- 49. A recombinant transfection system, comprising
 - (i) a gene construct encoding a cell-cycle regulatory (CCR) protein and operably linked to a transcriptional regulatory sequence for causing expression of the CCR-protein in eukaryotic cells, the CCR-protein being characterized by an ability to bind to inhibit activation of cyclin dependent kinase, and
 - (ii) a gene delivery composition for delivering the gene construct to a cell and causing the delivery composition for delivering the gene construct.



- 50. The recombinant transfection system of claim 52, wherein the gene delivery composition is selected from a group consisting of a recombinant viral particle, a liposome, and a poly-cationic nucleic acid binding agent,
- 51. A method of determining if a subject is at risk for a disorder characterized by unwanted cell proliferation, comprising detecting, in a tissue of said subject, the presence or absence of a genetic lesion characterized by at least one of

a mutation of a gene encoding a protein represented by SEQ ID No. 4, or a homolog thereof; and the mis-expression of said gene.

- 52. The method of claim 51, wherein detecting said genetic lesion comprises ascertaining the existence of at least one of
 - i. a deletion of one or more nucleofides from said gene,
 - ii. an addition of one or more nucleotides to said gene,
 - iii. an substitution of one or more nucleotides of said gene,
 - iv. a gross chromosomal rearrangement of said gene.
 - v. a gross alteration in the level of a messanger RNA transcript of said gene,
 - vi. the presence of a non-wild type splicing pattern of a messanger RNA transcript of said gene, and
 - vii. a non-wild type level of said protein.
- 53. The method of claim 51, wherein detecting said genetic lesion comprises
 - providing a probe/primer comprising an oligonucleotide containing a region of nucleotide sequence which hybridizes to a sense or antisense sequence of SEQ ID No. 3 or naturally occurring mutants thereof or 5' or 3' flanking sequences naturally associated with said gene;
 - ii. exposing said probe/primer to nucleic acid of said tissue; and
 - iii. detecting, by hybridization of said probe/primer to said nucleic acid, the presence or absence of said genetic lesion.
- 54. The method of claim 53, wherein detecting said lesion comprises utilizing said probe/primer to in a polymerase chain reaction (PCR).
- 55. The method of claim 53, wherein detecting said lesion comprises utilizing said probe primer in a ligation chain reaction (LCR).

- The method of claim 52, wherein the level of said protein is detected in an 56. immunoassay.
- A method of determining a risk of cellular transformation of a cell, comprising 57. detecting in the cell the presence of a protein complex between cyclin dependent kinase (CDK) and a p15 protein having an amino acid sequence represented by SEQ ID No. 4, or a homolog thereof.